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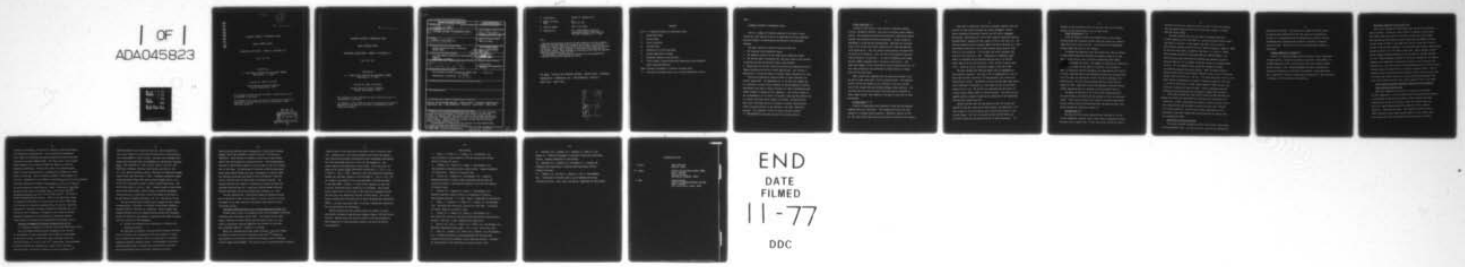

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ANNUAL PROGRESS REPORT

RESPONSIBLE INVESTIGATOR: HERBERT B. HECHTMAN, M.D.

April 30, 1977

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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Positive end expiratory pressure has been found to (1) alter pulmonary metabolism activity because of increased lung stretch; (2) cause the release of a humoral agent which gains access to the systemic and coronary circulation; (3) produce a decrease in left ventricular contractility and cardiac output. These findings are reported in both dogs and patients suffering acute respiratory failure.

The entrappment of granulocytes and platelets has been demonstrated in animals and man with respiratory failure.

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Part I.

Positive end expiratory pressure has been found to (1) alter pulmonary metabolism activity because of increased lung stretch; (2) cause the release of a humoral agent which gains access to the systemic and coronary circulation; (3) produce a decrease in left ventricular contractility and cardiac output. These findings are reported in both dogs and patients suffering acute respiratory failure.

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CONTENTS

PART I.

PULMONARY RESPONSE TO HEMORRHAGIC SHOCK

This is a summary of research conducted in the past 1½ years. During this time interval a series of experiments have been completed which are helpful in understanding the hazards of end expiratory pressure.

The major conclusions deriving from these data are:

1. The lungs are active metabolic organs
2. The metabolic function of the lungs may be altered by stretch
3. The various agents released by the lungs gain access to the systemic circulation and may significantly affect organ function
4. Specifically it has been found that positive end expiratory pressure induces biventricular failure in both dogs and man. This failure is mediated by a circulating negative inotropic agent released by the lungs.

Positive end expiratory pressure (PEEP) is known to depress the cardiac output (CO). The phenomenon has in the past been thought due to a decrease in venous return secondary to high intrapleural pressures. Experimental work done in normal volunteers in 1943 by Cournand provided strong evidence in support of this hypothesis. Our initial studies of the cardiodynamics of critically ill patients requiring PEEP yielded data at variance with these early studies of Cournand. We observed that PEEP almost inevitably led to an increase in central venous pressure (CVP) in contradistinction to the decrease in net CVP*, reported by Cournand. This prompted a series of animal and human studies.

* net pressure is measured pressure minus pleural pressure

Closed Chest Dogs (1)

A group of nine animals, closed chested, underwent pulmonary arterial, peripheral arterial, left atrial and pleural space catheterization. Net transmural pressures were derived by subtracting pleural pressure from measured intravascular pressures. Cardiac output was determined in triplicate by thermodilution. When PEEP was increased from 0 to 15 cm H_2O, the cardiac index (CI) fell from 108 ml/min·Kg to 82 ml/min·Kg ($p < .05$), net central venous pressure increased from 5.2 mm Hg to 8.4 mm Hg ($p < .01$), net left atrial pressure increased from 6.8 mm Hg to 7.3 mm Hg ($p < .1$) and net pulmonary artery wedge pressure (PAWP) increased from 6.7 mm Hg to 9.5 mm Hg ($p < .02$). These data suggest (1) the occurrence of biventricular failure and (2) that these animals were not suffering a primary decrease in venous return to the right heart.

Other authors have suggested that the observed elevation in CVP was due to right ventricular failure induced by PEEP. The mechanism of this failure was thought to be a decrease in the cross section area of the vascular bed and elevated pulmonary artery pressure. The fact that net left atrial pressure (LAP minus pleural pressure) in these closed chested dogs tended to rise made us suspicious of these conclusions.

No Chest Dogs (1, 2)

A series of experiments were conducted in dogs who had undergone complete chest wall resections. This preparation assured the maintenance of a constant pleural pressure. Mechanical effects of PEEP on the veins of the chest and on the coronary circulation were removed.

Eight dogs on mechanical ventilation underwent complete chest wall excision so that pleural pressure was always atmospheric. Central venous, pulmonary and systemic arterial and left atrial catheters were placed. Application of 15 cm of PEEP caused a significant drop in-theromodilution measured CO from a mean of 3.03 to 2.06 L/min ($p < .01$) and mean systemic arterial pressure (MAP) from 105 to 69 mm Hg ($p < .001$). Concurrently, there was a rise in mean central venous pressure (CVP) from 5.5 to 8.3 mm Hg ($p < .01$) and mean left atrial pressure (LAP) from 6.3 to 8.0 mm Hg ($p < .03$). Tightening of a pulmonary artery choker to reproduce the elevated PAP observed with 15 cm of PEEP, from a mean of 18.0 to 24.4 mm Hg ($p < .001$), failed to cause a drop in CO. There was also no significant change in CVP, LAP or MAP.

The data indicate that PEEP may depress the CO independent of intra-thoracic pressure. This drop in CO is accompanied by a rise in both right and left ventricular filling pressures, the criteria for biventricular failure. Furthermore, CO does not drop when right ventricular afterload is increased to a level equal to that at which PEEP caused a fall in CO. The results are consistent with the action of a neural and/or humoral agent on cardiac function. The results do not support previous concepts concerning the mechanisms of the hemodynamic abnormalities induced with PEEP.

Despite the fact that the same amount of PEEP (15 cm H_2O) was applied to both the closed and no-chest animals, the depression in CO and increase in filling pressures were significantly greater in the no-chest group. This led us to theorize that the PEEP effect was primarily related to lung stretch and not to applied pressure. The

absence of the restraining effect of the chest wall led to markedly greater resting lung volumes in the no-chest group.

Cross Circulation (3, 4)

Since the lungs are known to be metabolically active organs, we postulated that pulmonary stretch caused the release of a humoral agent that led to cardiac failure. In the next set of experiments strong support was given to this concept.

To examine the hypothesis that the biventricular failure induced by PEEP could be humorally mediated, we studied a group of 16 dogs (eight pairs) using a cross circulation preparation where 300 ml blood was exchanged per minute. One member of each pair was arbitrarily designated as donor and the other as recipient. The recipient's PAWP was maintained constant throughout the experiment by the infusion of fluid. When the donor's end expiratory pressure was increased from 0 to 15 cm H_2O, the recipient's CO fell from 95.2 ml/min·Kg to 74.1 ml/min·Kg ($p < .01$) and returned towards baseline levels with the removal of PEEP. These data confirm the hypothesis that PEEP induces cardiac depression which is mediated in part by humoral factors.

The degree of decrease in CO in the animal treated with PEEP was significantly correlated with the decrease in CO in the untreated animal. These results indicate the release of a humoral agent whose cardiac effects could be both qualitatively and quantitatively transferred through the circulatory system (1).

Isolated Heart (5)

The nature of this cardiac depression was examined in a series of nine completely isolated, paced, canine hearts, undergoing coronary perfusion from a support dog. A left ventricular balloon was used to

construct Starling and compliance curves at each of three time periods: when the support dog was placed on 0 cm H_2O PEEP, ($ZEEP_1$), 15 cm H_2O PEEP and finally $ZEEP_2$.

The mean coronary flow rate was fixed at 141 ml/min·100 gm ± 10 SEM (standard error of the mean) at a perfusion pressure which ranged from 105 to 111 mm Hg. In the support dog, PEEP led to a fall in mean arterial pressure from 116 mm Hg ± 7 SEM to 70 mm Hg ± 7 SEM ($p < .005$). CO fell from 4.69 l/min ± 0.4 SEM to 2.00 l/min ± .11 SEM ($p < .0005$). These changes reverted to normal when PEEP was removed ($ZEEP_2$). The Starling curves were constructed by plotting peak generative systolic pressure (PSP) at 5 ml increments of balloon volume, to a maximum volume of 60 ml. At the highest balloon volume PSP averaged 127 mm Hg and diastolic pressure 25.5 mm Hg ($ZEEP_1$). When the support dog was placed on PEEP, PSP was significantly reduced at each of the six inflation volumes from 25 to 50 ml ($p < .05$ to $p < .01$ using the paired t test, $n = 9$). These volumes corresponded to a range in diastolic pressure of 5.6 mm Hg ± 1.4 SEM to 18.8 mm Hg ± 1.7 SEM. After removal of PEEP, the Starling curves were identical to those at $ZEEP_1$. Cardiac compliance and mean coronary perfusion pressures were unchanged at $ZEEP_1$, PEEP and $ZEEP_2$.

These data indicate that lung stretch induced by PEEP stimulate the release of a blood born agent which will decrease left ventricular contractility. Further, the absence of change in coronary vascular resistance indicated that the decrease in contractility was not a function of coronary perfusion. This was more strongly confirmed by a 15 μ microsphere study which showed that the distribution of coronary flow was unchanged with PEEP.

Definition of Circulating Agent

It has been strongly suspected that the active humoral agents were the prostaglandins (PG). An infusion of PGE produced the cardiodynamic

effects seen with PEEP. Preliminary data suggest that PEEP induces PG release and/or metabolism by the lung since the PG metabolites 15 keto, 13, 14 dehydro PGE and PGF (measured by a specific antibody radioimmune assay technique) were markedly increased in pulmonary venous effluent. The precise role of the prostaglandins remains to be defined.

Cardiac Depression in Humans (6)

Finally, in order to demonstrate the practical clinical importance of these results, a group of 9 patients was studied. During PEEP, all suffered decreases in CO. Four had chest tubes and in these patients net CVP rose ($p < .01$). Echocardiography was used to evaluate left ventricular dimensions in the other five patients. During PEEP there was a significant increase in end diastolic diameter ($p < .05$) indicating a decrease in left ventricular contractility.

Myocardial Depression During Sepsis (7)

The cardiac response to volume loading was evaluated in 50 severely septic patients. Following a rapid infusion of albumen or whole blood the cardiac index (CI) and left ventricular stroke work index (LVSWI) were recorded as the pulmonary arterial wedge pressure (PAWP) increased. Initial values of PAWP, CI and LVSWI were similar in both the 19 surviving and 31 non-surviving patients. Surviving patients, however, demonstrated greater increases in CI and LVSWI as PAWP rose. Nearly one-half of both patient groups developed decreases in CI and LVSWI as the PAWP continued to rise. These downslopes occurred at relatively low PAWP and are taken as evidence of an abnormality of myocardial function in both survivors and non-survivors. The lower upslope of the performance curves in non-survivors indicates myocardial depression or a negative inotropic effect. Cardiac ischemia, acute respiratory failure and high affinity red cells were found to diminish the cardiac response to volume loading whereas hepatic and renal failure were associated with a good response of the CI and LVSWI.

Fluid Loading to Reverse Myocardial Depression During Abdominal Aortic Aneurysm Resection (8)

Myocardial depression during aortic clamping and declamping has been suggested as a cause of hypotension following aortic declamping. To investigate and manage this problem, thermal dilution Swan-Ganz catheters were placed in 22 elderly, high risk patients (mean age 70.8 $\pm$ 6.7 years) undergoing elective abdominal aortic aneurysm resection. There were no deaths. Mean systemic arterial pressure (MAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), and cardiac index (CI) were determined preoperatively, following

induction of anesthesia, during aortic clamping, following declamping, and 12-48 hours postoperatively. Starling myocardial performance curves (MPC) were determined by measuring PAWP and CO before and after infusion of salt-poor albumen (SPA). The slope of this curve (cardiac output response to an increase in PAWP) was taken as an index of myocardial performance. Patients were found to be relatively hypovolemic 12 hours preoperatively as evidenced by a uniformly low PAWP (4.02 ± 2.36 mm Hg). SPA was infused to maintain a PAWP between 5 to 10 mm Hg. Preoperative CI at a PAWP of 10 mm Hg (CI_{10}) was 3.41 ± 0.73 l/min·m^2. Following induction of anesthesia CI_{10} decreased to 2.52 ± 0.53 l/min·m^2 and this decrease was significant ($p < .002$). There was no significant change with the aorta cross-clamped ($CI_{10} + 2.41 \pm 0.53$ l/min·m^2). Following declamping CI_{10} rose to 3.13 ± 0.48 l/min·m^2. The slope of the MPC followed this same pattern. There was no significant change in preoperative MAP (98.3 ± 17.6 mm Hg) with the aorta clamped (99.8 ± 21.0 mm Hg) or following declamping ($98.0 \pm 18.$ mm Hg). Myocardial performance is depressed following induction of anesthesia but is not altered by aortic clamping or declamping in this group of patients. Declamping hypotension can be minimized or prevented by optimum volume loading as guided by Starling myocardial performance curves.

Pulmonary Entrapment of Platelets and White Cells (9, 10)

a) Pulmonary Entrapment of Platelets During Acute Respiratory Failure

The relationship between platelet entrapment by the lung and the development of acute respiratory failure (ARF) was investigated in two groups of dogs, treated either with intravenous oleic acid (OA) 0.075 ml/Kg, or E. coli, 2.76×10^{11} organisms/Kg. Lung entrapment of normal platelets was determined by a double tracer indicator dilution method: the tracers injected were normal autologous Cr^{51}

labelled platelets and indocyanine green dye. The resultant dilution curves allowed the calculation of the percent of injected platelets recovered(RP) in arterial blood. Two hours after treatment with either agent the physiologic shunt ($\dot{Q}_S/\dot{Q}_T$) was significantly increased: $\dot{Q}_S/\dot{Q}_T$ = 28.3 after OA ($p < .001$) and 25.2 after E. coli ($p < .01$). Physiologic deadspace increased significantly only after E. coli ($p < .01$), whereas pulmonary vascular resistance and compliance changed significantly only after OA ($p < .001$). Pathologic examination showed severe hemorrhagic edema after OA but minimal changes after E. coli. The RP fell from baseline values of 92.2% to 83.0% after OA ($p < .02$) and to 75.4% after E. coli ($p < .001$). Platelet counts in mixed venous and arterial blood showed a similar degree of platelet entrapment. Finally there was a significant correlation between the decrease in RP and increase in $\dot{Q}_S/\dot{Q}_T$ following E. *coli* ($p < .02$) but not for OA.

The data indicate that platelets may be trapped by lungs showing increased $\dot{Q}_S/\dot{Q}_T$. Entrapment is unrelated to physiologic deadspace, pulmonary vascular resistance or compliance. Results suggest that damaged endothelium and not damaged platelets produce the entrapment. Factors in addition to lung damage as observed at the light microscopic level are involved in this phenomenon.

b) Platelet and Leukocyte Lung Interactions in Patients with Respiratory Failure

The importance of pulmonary interaction with platelets and leukocytes in inducing acute respiratory failure was studied in a group of 23 severely septic patients and in a second group of 12 patients undergoing abdominal aneurysm surgery. The entrapment of platelets and WBC by both groups of patients were significantly correlated. Only the neutrophils were consistently removed by the lungs.

Septic patients exhibited severe derangements in physiologic shunting ($\dot{Q}S/\dot{Q}_T$), physiologic deadspace, pulmonary vascular resistance and compliance. These measures of pulmonary function were significantly poorer than the postoperative aneurysm patients. The thrombocytopenia observed in both patient categories did not relate to the loss of platelets in the lungs. The percentage of platelets or WBC in mixed venous blood, which passed through the lungs, and appeared in arterial blood was inversely correlated with $\dot{Q}S/\dot{Q}_T$ in septic patients ($p < .001$) but did not correlate with any other aspect of pulmonary function. The aneurysm patients also showed no correlation of platelet and WBC with pulmonary function (save for a surprising relation between increased platelet entrapment and decreased physiologic deadspace, $p < .05$.)

The data substantiate a relationship between the pulmonary entrapment of platelets or WBCs and the hypoxia of sepsis, but fail to relate entrapment to any other functional abnormality associated with acute respiratory failure.

The Value of Portable Chest X-ray in Acute Respiratory Failure (11)

Portable chest x-rays are customarily used in the assessment of patients suffering acute respiratory failure (ARF). The ability of this radiographic technique to define several manifestations of ARF, i.e., the amount of physiologic shunting ($\dot{Q}_S/\dot{Q}_T$) and the presence of non-cardiogenic pulmonary edema was studied in 11 patients.

$\dot{Q}_S/\dot{Q}_T$ was calculated during 50% oxygen breathing. Lung water (PEVW) was measured using the tracers indocyanine green and I^{131}-antipyrine. Left ventricular end diastolic pressure was estimated from the pulmonary arterial wedge pressure (PAWP). Thirty-seven sets of observations were recorded.

Repeat studies in the same patient were done at one to three day intervals. Portable chest x-rays were performed at the time of the physiologic observations and were interpreted by three independent radiologists. The films were graded from zero to four for the presence of: pulmonary edema and left ventricular failure (LVF). The x-ray scores for edema did not predict $\dot{Q}_S/\dot{Q}_T$ (correlation coefficient, $r = .17$, $p < .1$), or PEVW ($r = .30$, $p < .08$). There was a poor but significant correlation between the radiologic diagnosis of LVF and PAWP ($r = .44$, $p < .01$). LVF was thought to be present in 14 x-rays when PAWP < 15 mm Hg and absent in two (when PAWP > 15 mm Hg. In each of four patients, at least one x-ray was incorrectly read as normal for all variables. Two of these errors occurred late in the course of ARF calling into question the concept that the x-ray abnormality lags the clinical course. All x-rays read as abnormal were associated with at least one physiologic abnormality ($\dot{Q}_S/\dot{Q}_T > .15$, PEVW >120 ml/m^2, PAWP > 15 mm Hg), although not necessarily the one specified by the radiologists.

Results indicate that the portable chest x-ray offers no useful quantitative information regarding gas exchange, edema or left ventricular function. When positive, the x-ray was useful in calling attention to some abnormality in cardio-pulmonary function, but could not specify the abnormality.

PUBLICATIONS

1. Manny, J., Patten, M.T., Liebman, P.R. and Hechtman, H.B.: The association of lung distention, PEEP and biventricular failure. Annals of Surgery (In press).

2. Liebman, P.R., Patten, M.T., Manny, J. and Hechtman, H.B.: The mechanism of depressed cardiac output on PEEP. Surgery (Submitted for publication). Abstract to Surgical Forum

3. Patten, M.T., Liebman, P.R. and Hechtman, H.B.: Humorally mediated decreases in cardiac output associated with positive end expiratory pressure. Microvascular Research 13:137-139, 1977 Abstract to Surgical Forum.

4. Patten, M.T., Liebman, P.R., Manny, J. and Hechtman, H.B.: Humorally mediated cardiac failure as a consequence of positive end expiratory pressure. J. of Appl. Physiol. (Submitted for publication)

5. Manny, J., Staunton, P., Patten, M.T., Liebman, P.R. and Hechtman, H.B.: Decreased left ventricular contractility with PEEP. Circulation (In press). Abstract to Surgical Forum

6. Patten, M.T., Liebman, P.R., Manny, J. and Hechtman, H.B.: Left ventricular failure in patients treated with positive end expiratory pressure. New Engl. J. Med. (Submitted for publication)

7. Weisel, R.D., Vito, L., Dennis, R.C., Valeri, C.R. and Hechtman, H.B.: Myocardial depression during sepsis. Am. J. Surg. 133:512-521, 1977.

8. Bush, H.L., Logerfo, F.W., Weisel, R.D., Mannick, J.A. and Hechtman, H.B.: Optimum intravascular volume management with the Swan-Ganz catheter during elective abdominal aortic aneurysm resection. (Accepted for presentation at the International Vascular Society, 1977)

9. Hechtman, H.B., Lonergan, E.A., Staunton, P., Dennis, R. and Shepro, D.: Pulmonary entrapment of platelets during acute respiratory failure. Surgery (Submitted for publication)

10. Hechtman, H.B., Lonergan, E.A. and Shepro, D.: Platelet and leukocyte lung interactions in patients with respiratory failure. Surgery (In press).

11. Liebman, P.R., Phillips, E., Weisel, R., Ali, J. and Hechtman, H.B.: Limitations of portable chest x-ray in patients with acute respiratory failure. Surg. Gynec. and Obstet. (Submitted for publication)

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